Short-term effects of menthol on walking dyspnoea in patients with COPD: a randomised, single blinded, cross-over study

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To the Editor:

Exertional respiratory discomfort is the most common symptom in patients with COPD [1]. Menthol has recently been proposed as an ergogenic aid to decrease the perception of dyspnoea during exercise [2–4]. Menthol activates the transient receptor potential melastatin 8 (TRPM8) channels in the sensory nerve fibres of the tongue, promoting a feeling of freshness and a cognitive illusion of airflow into the airways [2, 5, 6]. We hypothesised that chewing menthol-flavoured gum before exercise would decrease the perception of dyspnoea during walking in COPD patients.

We conducted a randomised, cross-over, multicentre trial (Groupe Hospitalier du Havre, center hospitalier de Morlaix, center Resp'Air Talence) (ClinicalTrials.gov identifier: NCT03626519). Inclusion criteria were diagnosis of COPD (per Global Initiative for Chronic Obstructive Lung Disease guidelines), participation in a pulmonary rehabilitation programme, functional dyspnoea (modified Medical Research Council (mMRC) scale $\geqslant$2) and consent to participate. Exclusion criteria were clinical instability (pH <7.35 or body temperature >38°C), neurological/orthopaedic disorders, difficulty with chewing and swallowing disorders.

Participants performed the 6-min walk test (6MWT) once during the baseline assessment for familiarisation. On the test day (between 2 and 5 days after the baseline assessment), they performed two 6MWT, separated by 30 min of rest, in two different, randomised conditions. In the experimental condition, participants chewed menthol-flavoured gum (Airwaves Extreme Menthol Extreme, Wrigley, Chicago, IL, USA) for 5 min before the test and in the control condition, they chewed strawberry-flavoured gum (Hollywood Strawberry Style, Mondelēz International, Uxbridge, UK). No encouragement was given during the 6MWT to avoid influencing participants.

The primary outcome was end-of-task dyspnoea measured using the modified 0–10 Borg scale (0=no dyspnoea, 10=maximal dyspnoea).

Secondary outcomes were end-of-task leg discomfort (0–10 Borg scale), peripheral oxygen saturation, heart rate, tidal volume, minute ventilation, inspiratory capacity and respiratory rate (measured using Spirodoc (Medical International Research, Rome, Italy)), and 6-min walking distance. After completion of both tests, participants were asked which condition they had preferred and if they felt that the menthol had had any effect.

A randomisation sequence was determined for each centre by the research unit using Edgar2 (www.Edgarweb.Org.Uk/) computer software (ratio 1:1). The randomised condition sequence was provided in a closed, opaque envelope with the patient's inclusion number on the front and opened by a research assistant just before the first condition. Participants could not be blinded; however, their knowledge of the purpose of the study was limited to "the impact of menthol on effort". Assessors were blinded to the condition. This was ensured by: 1) the participant chewing the gum in a closed room while the assessor waited at the test site; and 2) the assessor remaining at a minimum distance of 2 m from the participant to avoid smelling their breath. 63 participants were required to detect a between conditions difference of 1 point on the modified Borg scale 0–10 (minimal clinically important difference) [7] and a moderate effect size (0.5) on end-of-task dyspnoea with a power of 80% and an alpha risk $\leqslant$0.05.

Shareable abstract (@ERSpublications)
Chewing menthol gum prior to exercise is a safe, easy-to-implement, low-cost, non-pharmacologic intervention that provides a reduction in dyspnoea in a third of patients and decreases the perception of discomfort during exercise in two-thirds of patients https://bit.ly/3FoFHp1

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Mean differences were calculated using a mixed model adjusted for baseline values, and the sequence (order of conditions) was used to assess the carry-over effect, with participants as random effects. R-software was used (https://www.R-project.org/) with the packages lme4 and lmerTest [8–10]). Statistical analysis was performed blind.

This study was approved by the French Ethics committee Sud-Est 6 (17 May 2018). Written informed consent was obtained from all patients.

63 patients were included between October 2019 and February 2021 (male/female ratio: 38/25, mean±SD age: 68±20 years and mean±SD body mass index: 27±7 $kg \cdot m^{-2}$). Patients had severe bronchial obstruction (mean±SD forced expiratory volume in 1 s (FEV_1): 44±15% predicted; mean±SD forced vital capacity: 76±18% predicted) and lung hyperinflation (mean±SD residual volume: 166±50% predicted; mean±SD total lung capacity: 110±19% predicted; mean±SD inspiratory capacity: 77±23% predicted). All participants had functional dyspnoea (mean±SD mMRC 2.4±0.6) and their COPD significantly impacted on their performance of activities of daily living (St George's Respiratory Questionnaire – activities limitations mean±SD 68±20%; scores range from 0 to 100, higher scores indicate more severe limitations).

A trend towards reduced dyspnoea with menthol was observed, but the benefits were trivial (table 1). The lower bound of the confidence interval did not reach the minimal clinically important difference of 1 point on the modified Borg scale [11]. However, analysis of individual data showed that the menthol reduced dyspnoea by at least 1 point in 21 participants (33%). 40 participants (63%) reported a positive effect of the menthol on their exercise tolerance. Only two participants reported having worse dyspnoea in the menthol condition. No between condition differences were observed for the secondary outcomes (table 1). For leg discomfort, there was evidence of a period or cross-over effect (p=0.050), this result should therefore be interpreted with caution. There was no evidence of a period or carry-over effect for any of the other outcomes. No baseline characteristic identified responder patients; however, the confidence interval showed a trend that patients with FEV_1 <35% predicted were more likely to respond (relative risk 1.67 (95% CI 0.87–3.21) p=0.16).

Cooling sensations have previously been shown to reduce dyspnoea. For example, breathing fresh air (7°C) modestly decreased dyspnoea and increased peak exercise performance in patients with COPD [12]. Menthol can provide a cooling sensation by stimulating the membrane bound ion channel, TRPM8, inducing a perceived reduction in temperature within the range of 8–28°C [4]. This cooling sensation could increase the cognitive inspiratory flow and may alter the emotional and affective perception of dyspnoea [2].

TABLE 1 Effects of menthol gum *versus* control gum on dyspnoea and physiological variables at the end of exercise

Variables	Menthol		Control		Condition effect	
	Baseline	End-exercise	Baseline	End-exercise	Adjusted mean difference[#]	p-value
Dyspnoea, mBorg	0.9±1	4.4±1.6***	1±1.0	4.7±1.7***	−0.3 (−0.5–−0.0)	0.058
Leg discomfort, mBorg	0.6±1.1	2.8±2.1***	0.6±1	2.9±2.3***	−0.0 (−0.3–0.2)	0.807
S_{pO_2}, %	92.6±3.7	85.7±7***	92.6±3.3	86.3±6.2***	−0.4 (−1.0–0.3)	0.255
Lowest S_{pO_2}, %		82.7±7.3		83.1±6.6	−0.4 (−1.2–0.3)	0.263
Heart rate, beats per min	91.4±17.8	115.3±15.2***	92.3±17.5	114.5.9±15.7***	4.4 (−1.2–9.9)	0.124
Respiratory rate, cycles per min	18.6±4.6	24.1±9.5***	19±5.2	24.1±5.9 ***	0.3 (−2.1–2.6)	0.827
Tidal volume, L	0.8±0.3	1.1±0.5 ***	0.8±0.4	1.1±0.5***	0.0 (−0.0–0.1)	0.172
Minute ventilation, $L \cdot min^{-1}$	13.9±5.1	25.6±9.3***	14.7±5.6	25.8±9***	−0.1 (−1.5–1.3)	0.924
Inspiratory capacity, L	1.8±0.6	1.7±0.6**	1.9±0.7	1.8±0.7	−0.0 (−0.2–0.1)	0.449
6MWD, m		461.1±124.2		458.7±124.9	2.6 (−4.1–9.4)	0.447
6MWD, % pred		73.1±20.7		72.8±20.7	0.37 (−0.76–1.5)	0.495

Continuous data are presented as mean±SD and as mean (95% CI) for the difference between the two conditions. Mean differences were calculated using a mixed model adjusted for baseline values, and the sequence (order of conditions) was used to assess the carry-over effect, with participants as random effects. Within-condition changes (before-after test) were compared using a paired t-test. *: p<0.05; **: p<0.01; and ***: p<0.001 for before–after analysis of a condition. mBorg: modified Borg scale from 0 to 10 (0: no fatigue or dyspnoea, 10: maximal fatigue or dyspnoea). For leg discomfort, there was evidence for a period or cross-over effect (p=0.050), this result should be taken with caution. There was no evidence of a period or cross-over effect on the other outcomes. S_{pO_2}: oxygen saturation measured by pulse oximetry; 6MWD: 6-min walking distance. [#]: difference for menthol − control.

The results of the present study showed a clinically trivial effect of menthol on end-test dyspnoea compared with the control condition; however, the reduction in dyspnoea reached the minimal clinically important difference in one-third of the participants and two-thirds reported a positive effect on their exercise tolerance.

We propose two explanations for this small effect. First, the Borg scale may not be sufficiently sensitive to detect a between-condition difference. The study by Kanezaki *et al*. [2] found a reduction in physical and mental breathing effort, air hunger, breathing discomfort, anxiety, and fear during inspiratory resistive loaded breathing in patients with COPD following olfactive stimulation by L-menthol using the Multidimensional Dyspnea Profile scale. This reflects the self-reported perception of the patients in our study. Secondly, individuals often modify their level of exertion during self-paced exercise tests, based on their level of dyspnoea. This could also explain why other studies failed to show a benefit of non-pharmacological strategies on exertional dyspnoea using the 6MWT [13, 14]. High-intensity constant work rate endurance tests are more sensitive for the detection of the effectiveness of an intervention [3, 15, 16].

Although no carry-over effect of menthol was observed on dyspnoea, we do not know the duration of the effect of menthol and its potential impact on the next condition is not known. Future studies could perhaps include a washout period longer than 30 min between the two conditions.

Another explanation for the negative result is that the sensation of breathing comfort faded over the course of the test as the menthol effect dissipated: several participants reported that they mainly felt the benefit during the first few minutes of the test. Studies in athletes reported a stronger effect of repeated menthol use on dyspnoea and on performance [4]. The lack of an effect on ventilatory pattern is in line with the results of Kanezaki *et al*. [2].

This study addressed a new area of research, looking at alternative and pragmatic approaches to the management of breathlessness. Future studies should take the methodological limitations that we outlined into consideration to optimise future studies in this field.

This multicentre study has several strengths: the assessors were blinded to limit measurement bias and the instructions given to patients were standardised to limit a centre effect. Patients were unaware that the primary outcome was dyspnoea to minimise the influence on this outcome. We asked patients to be as honest as possible about how they felt about menthol, and to report both positive and negative aspects.

Chewing menthol gum prior to exercise is a safe, easy-to-implement, low-cost, non-pharmacological intervention that provides a clinically important reduction in dyspnoea in one third of patients and decreases the perception of discomfort during exercise in two-thirds of patients. Continuous release or repeated administration of menthol may have a greater effect on dyspnoea reduction throughout exercise [4].

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